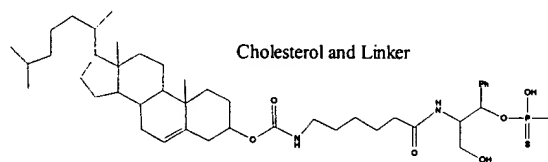


127	Chol-5'- d(ctgctAGC*C*TC*TGGAttga) <SEQ. ID. NO. 18>	P=S	82 mg	798 6	7993	PTEN
128	Chol-5'- d(cttctGGC*ATC*C*GGTttaga) <SEQ. ID. NO. 19>	P=S	84 mg	798 6	7994	PTEN

Note: (1) Chol: Cholesterol and Linker, see structure.

(2) t: 2'-O-MOE-rT; c: 2'-O-MOE-5-Me-rC;
a: 2'-O-MOE-rA; g: 2'-O-MOE-rG;
C*: 5-Me-dC



Please delete the Sequence Listing and replace it with the attached amended Sequence Listing.

REMARKS

The specification has been amended to correct inadvertent typographical errors. More specifically, Table 1 has been amended to correct the inadvertent omission of italics. Table 3 has been amended to correct several instances in which lower case letters, rather than upper case letters, were used in the oligonucleotide sequences. Table 9 has been amended to add a legend that was inadvertently omitted. Support for the amendments is found throughout the specification. No new matter has been added.

The Sequence Listing has also been amended to correct inadvertent typographical errors. More specifically, miscellaneous feature information that was inadvertently omitted has been added to sequences 3 to 10 and 12 to 19. In addition,

typographical errors in sequences 4 to 7 have been corrected. Support for the amendments is found in the specification at, for example, pages 47, 49, 50, 58, and 74 to 77. No new matter has been added.

Restriction Requirement

A restriction has been required under 35 U.S.C. § 121 to one of two groups of inventions, characterized as Groups I and II. The claims of each group, and the Office Action's interpretation of the subject matter associated with each group, are set forth below.

GROUP	CLAIMS	SUBJECT MATTER
I wherein	1-21 and 40-49	A process for preparing an oligonucleotide, said process comprises treating an extended oxidized compound to remove at least one phosphorous protecting group leaving at least one deblocked phosphorothioate linkage, and forming a 3'-functionalized compound.
II wherein	22-39 and 50-60	A process for preparing an oligonucleotide, said process comprises treating an extended oxidized compound with a reagent effective to de-block a protected hydroxyl group, thereby forming a 5'-functionalized compound.

The Office Action asserts that the inventions of Groups I and II are patentably distinct. In accordance with 37 CFR 1.143, applicants hereby provisionally elect for prosecution the subject matter of Group II (claims 22-39 and 50-60).

Election of Species Requirement

The Office Action requires that Applicants elect a single disclosed species for prosecution on the merits under 35 U.S.C. § 121 because searching all of the claimed species allegedly would be burdensome. Applicants submit, however, the subject matter recited in the present claims is such that a reasonable search would necessarily reveal any and all prior disclosures of claimed species, assuming that any exist. In this respect, it is noteworthy that the Office Action classifies the claims as relating to the same subclass and does not identify any evidence supporting the allegation that searching the claimed subject matter would be unduly burdensome. Accordingly, Applicants respectfully submit that a search and examination of the claimed methods would not impose a serious burden on the Examiner.

In accordance with 37 CFR 1.146, Applicants hereby elect for prosecution compound 120, which is depicted on page 70 of the specification as filed. It is Applicants' understanding that this election is being made solely to aid the Examiner in conducting a search and examination of the claimed subject matter, and is not to be construed as limiting the scope of Applicants' claims. It is Applicants' further understanding that, if the elected subject matter is found to be allowable over the prior art, the search and examination will be expanded to cover other species, until the examination includes the full scope of the claimed subject matter.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is requested respectfully.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

Date: August 13, 2002



Jane E. Inglese, Ph.D.
Registration No. 48,444

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439



DOCKET NO.: ISIS-4723

COPY OF PAPERS
ORIGINALLY FILED

PATENT

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Please delete the paragraph spanning page 47 of the specification and replace it with the following new paragraph.

Table 1. HPLC Retention Times for Oligonucleotides 8-31.

Compound	R	R ¹	Sequence, 5' to 3'	X ^a	Retention time, min ^b	
					Gradient 1	Gradient 2
8	TMT	H	T ₁₂ <SEQ. ID. NO. 1>	O	32.8	—
9	TMT	H	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	27.7	23.8
10	TMT	Pyr	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	—	30.2, 30.7
11	TMT	Pyr	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	O	—	29.1
12	TMT	Flu	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	33.4, 34.2	—
13	TMT	Flu	AGCT ₂ C T ₃ GCACA TGTA ₃ ^c <i>AGCT₂C T₃GCACA TGTA₃^c</i> <SEQ. ID. NO. 3>	S	35.9, 36.3	—
14	TMT	Flu	T ₁₂ <SEQ. ID. NO. 1>	O	32.9	—
15	TMT	C ₂ H ₅	T ₁₂ <SEQ. ID. NO. 1>	O	33.0	—
16	H	H	T ₁₂ <SEQ. ID. NO. 1>	O	18.0	—
17	H	H	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	19.6	16.4
18	H	Pyr	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	—	25.0
19	H	Pyr	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	O	—	24.5
20	H	Flu	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	23.4	—
21	H	Flu	AGCT ₂ C T ₃ GCACA TGTA ₃ ^c <i>AGCT₂C T₃GCACA TGTA₃^c</i> <SEQ. ID. NO. 3>	S	28.5	—
22	H	Flu	T ₁₂ <SEQ. ID. NO. 1>	O	22.7	—
23	H	C ₂ H ₅	T ₁₂ <SEQ. ID. NO. 1>	O	21.5	—
24	—	H	T ₁₂ <SEQ. ID. NO. 1>	O	16.2	—
25	—	H	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	18.0	15.2
26	—	Pyr	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	22.6	17.1
27	—	Pyr	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	O	22.0	16.7
28	—	Flu	ATGCAT ₂ CTGC ₃ A ₂ G ₂ A <SEQ. ID. NO. 2>	S	19.1	14.5
29	—	Flu	AGCT ₂ C T ₃ GCACA TGTA ₃ ^c <i>AGCT₂C T₃GCACA TGTA₃^c</i> <SEQ. ID. NO. 3>	S	21.7	—
30	—	Flu	T ₁₂ <SEQ. ID. NO. 1>	O	18.1	—
31	—	C ₂ H ₅	T ₁₂ <SEQ. ID. NO. 1>	O	17.9	—

^a All oligonucleotides contained uniform, either phosphate (X=O) or phosphorothioate (X=S) backbone; ^b For HPLC conditions, consult Experimental Procedures; ^c 2'-O-(2-methoxyethyl) ribonucleotide residues are italicized; C stands for 5-methyl-2'-O-(2-methoxyethyl)cytidine residue.

Please delete the paragraph spanning page 49 of the specification and replace it with the following new paragraph.

Table 3. ESMS data oligonucleotides 33–40.^a

	Sequence, 5' to 3'	Backbone	ESMS, found	Molecular Formula	ESMS, calculated
33	DMTr-TGCATC ₅ AG ₂ C ₂ AC ₂ A _t TpO <SEQ. ID. NO. 4>	P=O	6365.2	C ₂₁₁ H ₂₆₃ N ₇₁ O ₁₂₂ P ₂₀	6365.2
34	DMTr-TGCATC ₅ AG ₂ C ₂ AC ₂ A _t TpS <SEQ. ID. NO. 5>	P=O	6381.7	C ₂₁₁ H ₂₆₃ N ₇₁ O ₁₂₁ P ₂₀ S	6381.3
35	DMTr-TGCATC ₅ AG ₂ C ₂ AC ₂ A _t TpS <SEQ. ID. NO. 5>	P=S	6686.9	C ₂₁₁ H ₂₆₃ N ₇₁ O ₁₀₂ P ₂₀ S ₂₀	6686.5
36	TGCATC ₅ AG ₂ C ₂ AC ₂ A _t TpO <SEQ. ID. NO. 6>	P=O	6062.2	C ₁₉₀ H ₂₄₅ N ₇₁ O ₁₂₀ P ₂₀	6062.8
37	TGCATC ₅ AG ₂ C ₂ AC ₂ A _t TpS <SEQ. ID. NO. 7>	P=O	6079.4	C ₁₉₀ H ₂₄₅ N ₇₁ O ₁₁₉ P ₂₀ S	6078.9
38	TGCATC ₅ AG ₂ C ₂ AC ₂ A _t TpS <SEQ. ID. NO. 7>	P=S	6384.7	C ₁₉₀ H ₂₄₅ N ₇₁ O ₁₀₀ P ₂₀ S ₂₀	6384.2
39	TGCATC ₅ AG ₂ C ₂ AC ₂ ATpS-Pyr <SEQ. ID. NO. 8>	P=O	6350.9	C ₂₀₉ H ₂₅₈ N ₇₂ O ₁₂₀ P ₂₀ S	6350.2
40	TGCATC ₅ AG ₂ C ₂ AC ₂ ATpS-Flu <SEQ. ID. NO. 9>	P=O	6467.0	C ₂₁₂ H ₂₅₈ N ₇₂ O ₁₂₅ P ₂₀ S	6466.2

Please delete the paragraph spanning page 77 of the specification and replace it with the following new paragraph.

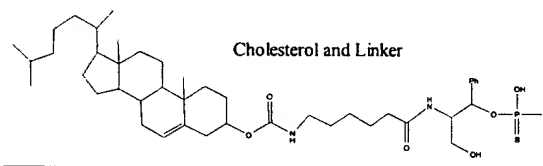
Table 9: Cholesterol-Conjugated Oligonucleotides (4)

Cmpd	Sequence (5' – 3')	Backbone	Quantity	MW	More
------	--------------------	----------	----------	----	------

				calc.	Found	Info
127	Chol-5'- d(ctgctAGC*C*TC*TGGAttga) <SEQ. ID. NO. 18>	P=S	82 mg	7986	7993	PTEN
128	Chol-5'- d(cttctGGC*ATC*C*GGTttaga) <SEQ. ID. NO. 19>	P=S	84 mg	7986	7994	PTEN

Note: (1) Chol: Cholesterol and Linker, see structure.

(2) t: 2'-O-MOE-rT; c: 2'-O-MOE-5-Me-rC;
a: 2'-O-MOE-rA; g: 2'-O-MOE-rG;
C*: 5-Me-dC



Please delete the Sequence Listing and replace it with the attached amended Sequence Listing.